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GUEST EDITORIAL

Sentinel Lymph Node Biopsy in Malignant Melanoma: The Standard of Care?

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The management of clinical Stage I melanomas and the role of lymphadenectomy in their management have been very controversial. Opinion varies from surgeons who advise immediate elective lymph node dissections for all patients with clinical Stage I melanoma to those who recommend observation alone for melanomas of intermediate thickness [1,2]. The main controversy always has been whether the potential morbidity of a lymphadenectomy is counterbalanced by the potential for therapeutic benefit. With thin melanomas, which are <0.75 mm in thickness, there is general agreement that patients do not require an elective lymph node dissection because their rate of lymphatic spread is very small and their prognosis is excellent when treated with local excision alone. Conversely, elective lymph node dissections may not be advisable for patients with thick melanomas (>4.0 mm) because the risk of systemic disease for this subgroup of patients may outweigh any potential benefit from elective lymph node dissection. This has led to the question of the role of elective lymph node dissection for intermediate thickness lesions. The questions to be asked are twofold. First, can survival be increased if micrometastatic disease is removed surgically before signs of distant metastases present themselves? Second, does the morbidity of lymphadenectomy, which has ranged from 5% to 25%, justify doing a procedure that has not yet been shown to be of significant benefit?

Advocates of elective lymph node dissection (ELND) for clinical stage I melanoma have theorized that early eradication of potential disease in the lymphatic bed can reduce the potential for distant metastases. This must be balanced against the potential morbidity of the lymph node dissection, which includes seroma formation, wound infection, flap necrosis, and nerve dysfunction. Long-term lymphedema of the lower extremity following groin dissection has been reported in ~26% of cases and caused a significant functional deficit in 8% of patients [3–5].

Does ELND increase patient survival? Retrospective data [6] suggested that for intermediate thickness lesions, there was a survival benefit. However, prospective randomized [7–9] studies have not demonstrated a survival benefit of ELND vs. DLNR (diagnostic lymph node resection) and therefore have not conclusively resolved the issue. A recent report [10] from a prospective, randomized cooperative group study looked at 742 melanoma patients with a median follow-up of 8.6 years. Although there was no overall survival difference, there was a significant improvement in overall survival in selected subgroups of patients who underwent ELND. This improvement in survival was shown for intermediate thickness lesions (1.1–2.0 mm) in patients 60 years of age and younger. From these reports it appears that the benefit of ELND is still ''marginal,'' so recent reports describing sentinel lymph node biopsy are of great interest.

The sentinel lymph node concept, first conceived and described by Morton et al, [11], is an innovative technique that eliminates the morbidity of lymphadenectomy for patients with ''negative'' sentinel nodes while selectively targeting those patients who are candidates for therapeutic lymphadenectomy. Intraoperative lymph node mapping permits the selective identification, removal, and histologic evaluation of the sentinel lymph nodes. These nodes can then be evaluated by rapid immunohistochemistry, frozen section, or PCR [12]. In Morton's' study [11] utilizing Isosulphan blue dye in clinical Stage I patients, at least one sentinel node was identified in ~82% of the lymph node specimens. In the majority of these patients (72%), a single sentinel lymph node drained a particular melanoma. There were 3,079 nodes identified in 194 lymphadenectomy specimens; of these, two nodes that were not identified as sentinel nodes were found to contain metastatic disease despite negative sentinel nodes. This was a false-negative rate of <1%. In terms of complications of the procedures, those

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that occurred were usually minor and of little long-term significance. Patients experienced some blue dye in their urine for the first 24 hours after the procedure, but there were no incidences of hypersensitivity reactions. Other postoperative complications included a 4% wound-edge necrosis rate, a 5.5% seroma rate, and a 4.8% infection rate.

The beauty of the sentinel node concept lies in both its simplicity and its accuracy. It allows the use of a minimally invasive procedure with minimal morbidity to document regional lymph node involvement with metastatic melanoma. Morton [11] has shown that only a limited number of lymph nodes are the initial recipients of metastatic melanoma cells. Follow-up studies have demonstrated a false negative rate of 4% and a predictive value of a negative sentinel lymph node of 98.5%. Initial work, performed using isosulphan blue dye injection, has now advanced to the use of Technetium 99 labeled sulfur colloid. Krag et al. [13] have described the use of a small, handheld gamma detector to locate the radioactive sentinel lymph node in the regional lymphatic basin. They were able to identify the sentinel node in 98% of their patients. Their results showed that for intermediate thickness lesions with clinically ''negative'' lymph nodes, the frequency of regional metastases was 23%. This is comparable to the frequency seen when complete lymphadenectomy was performed [14]. This last statement is extremely important because it supports the use of a minimally invasive technique to obtain similar data to those obtained from a much larger procedure.

At the recent Society of Surgical Oncology meeting, the combined experience of the M.D. Anderson Cancer Center and the Moffitt Cancer Center with lymphatic mapping was presented [15]: 600 patients who had undergone lymphatic mapping with a median follow-up of 20 months were analyzed. They reported that 2.8% of the patients who had been found to have a negative sentinel lymph node biopsy utilizing routine histology examination had subsequently developed nodal disease, with the previously mapped lymph node basin as the first site of failure. When the paraffin blocks were then re-examined using immunohistochemistry, 9 of the 12 patients were found to have microscopic disease in the sentinel node that had not been initially recognized. This then reduced the false negative rate to <1%.

If sentinel node biopsy is to be considered the standard of care, it must be able to be performed by the majority of practitioners in a standardized manner, and the results of the biopsy must contribute to decisions regarding the care of the patient. The technique of intraoperative lymph node mapping, especially with the use of the gamma probe, can be easily learned after 3–5 cases if one is tutored by someone familiar with the technique. The evaluation of the sentinel node via immunohistochemistry is available in most pathology departments. PCR techniques to detect tyrosine messenger RNA has yielded an increased detection of microscopic disease [12]. This latter technique may require specialized centers, but utilizing one or two sentinel nodes may be more cost effective than having to examine complete lymphadenectomy specimens.

In terms of contributing to optimal patient care, sentinel node biopsy allows the use of a minimally invasive procedure that will help decrease morbidity and may also allow more accurate staging. We now have a technique that seems to be cost effective and easy to perform. Information obtained influences patients care by reducing potential morbidity from treatment. For these reasons, sentinel lymph node biopsy should be considered the standard of care.

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